Quality Risk Management (QRM) and its Application

品質風險管理的理論與運用

Date: Jun2020
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Links 相關連結

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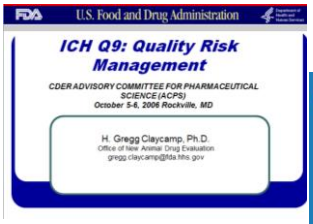

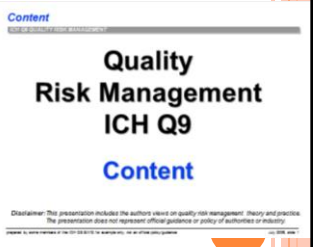

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Purpose of this talk 課程目的

- To guide through the content of the Quality Risk Management (ICH Q9 document).
- To provide some considerations, possible interpretations and where appropriate examples
- To practice risk assessment by using FMEA table

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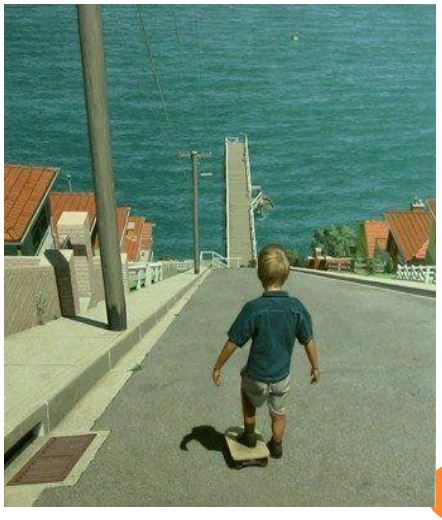
ICH Q9 QRM

品質風險管理介紹

1. Introduction – Risk management 風險管理

What is

Risk Management?



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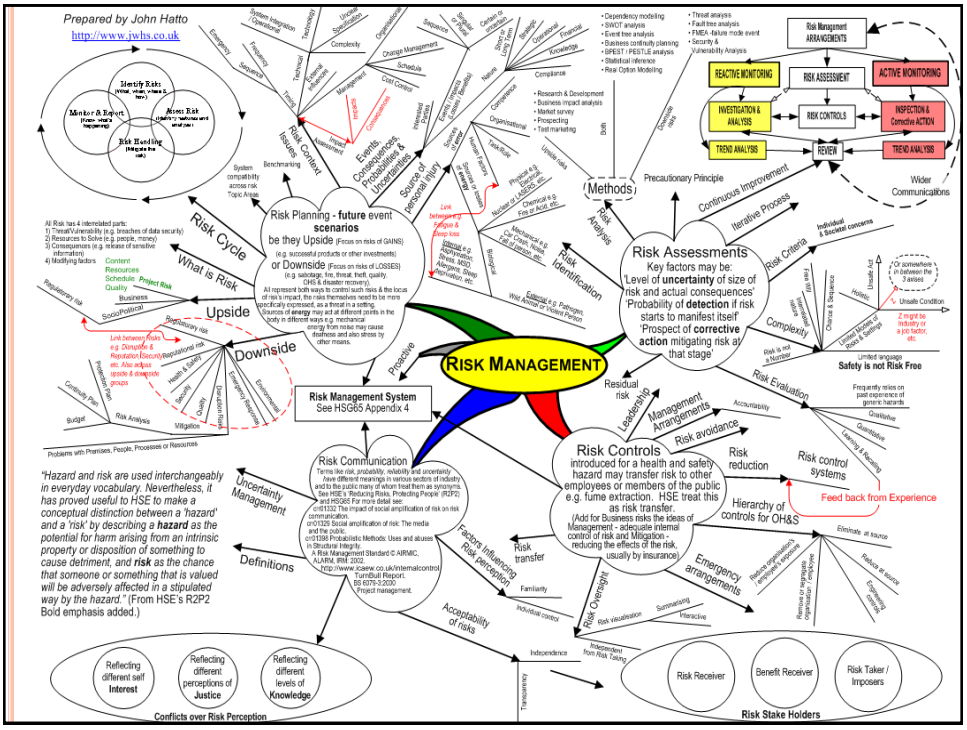

1. Introduction – ICH quality vision

"Develop a harmonised pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science." (ICH meeting Brussels , 2003)

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1. Introduction – ICH guideline

- Q1 Stability
- Q2 Analytical Validation
- Q3 Impurities
- Q4 Pharmacopoeias
- Q5 Quality of Biotechnological Products
- Q6 Specifications
- Q7 Good Manufacturing Practice
- Q8 Pharmaceutical Development
- **Q9 Quality Risk Management**
- Q10 Pharmaceutical Quality Systems

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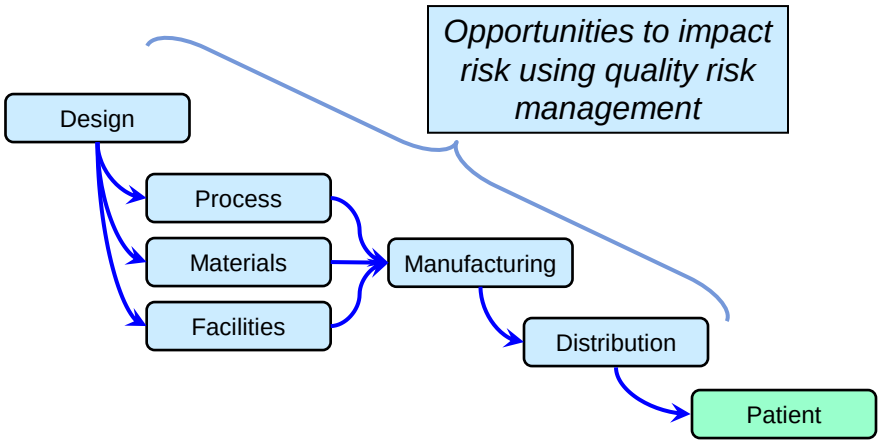
1. Introduction – Link to patient risk



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1. Introduction – Link to patient risk

- ICH Regulators:
  - **FDA: New paradigm with the 21st Century GMP initiative**
  - **EMEA: Revised EU directives**
  - **MHLW: Revised Japanese law (rPAL)**
- EU & Japan became involved at ICH GMP Workshop in July 2003: 5 year vision agreed:

  "*Develop a harmonised pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science*"
- Consequent ICH Expert Working Groups (EWG):
- **ICH Q8, on Pharmaceutical Development, doc. approved 2005**
- **ICH Q9, on Quality Risk Management, doc. approved 2005**
- **ICH Q10, on Quality Systems, topic accepted 2005**

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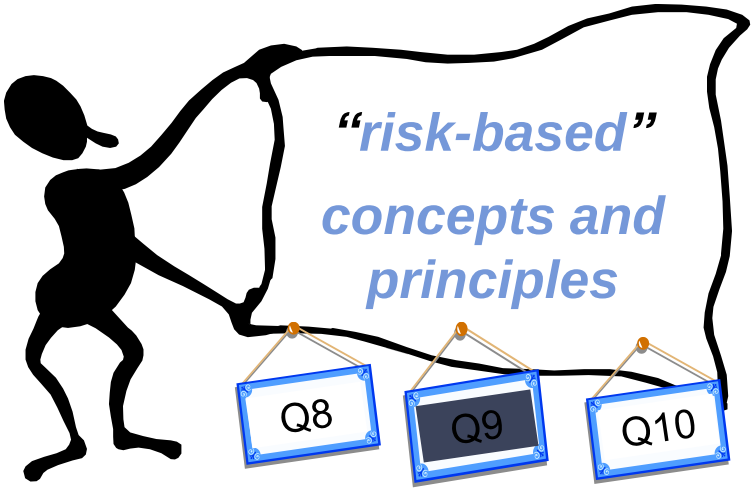
1. Introduction – The new paradigm



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1. Introduction – The new paradigm

Pharmaceutical Development (Q8)

Past:	Data transfer / Variable output
Present:	Knowledge transfer / Science based / consistent output

Quality Risk Management (Q9)

Past:	Used, however poorly defined
Present:	Opportunity to use structured process thinking

Pharmaceutical Quality Systems (Q10)

Past:	GMP checklist
Future:	Quality Systems across product life cycle

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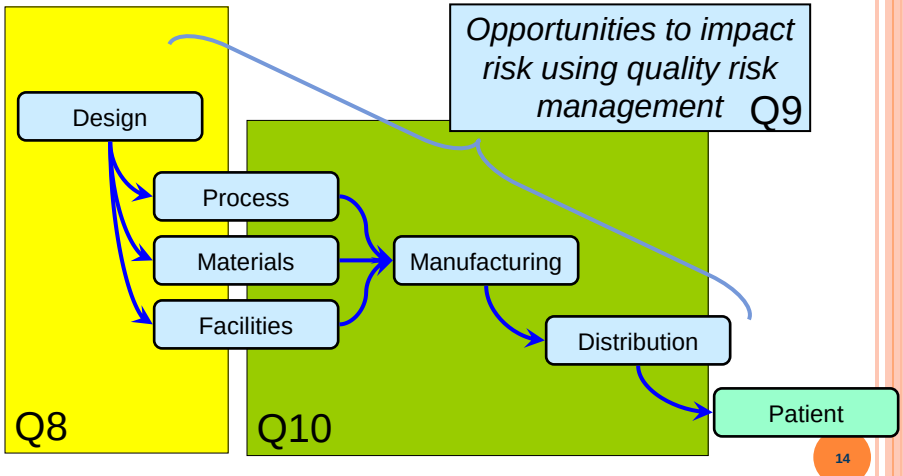
1. Introduction – ICH Q8, Q9, and Q10



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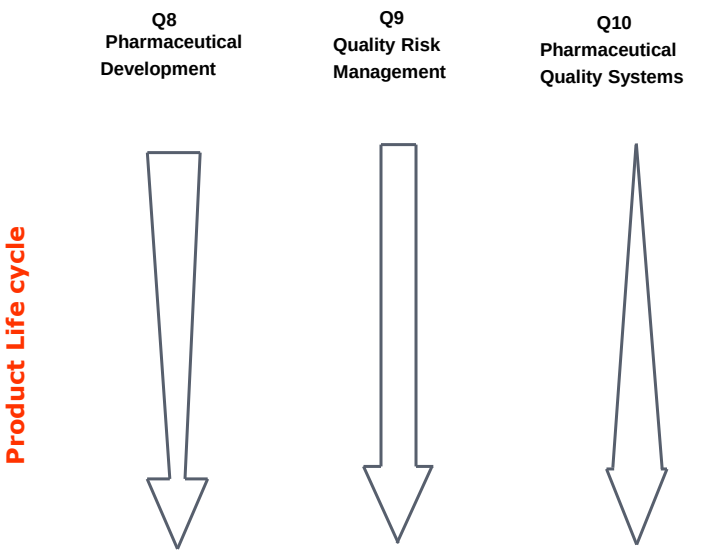
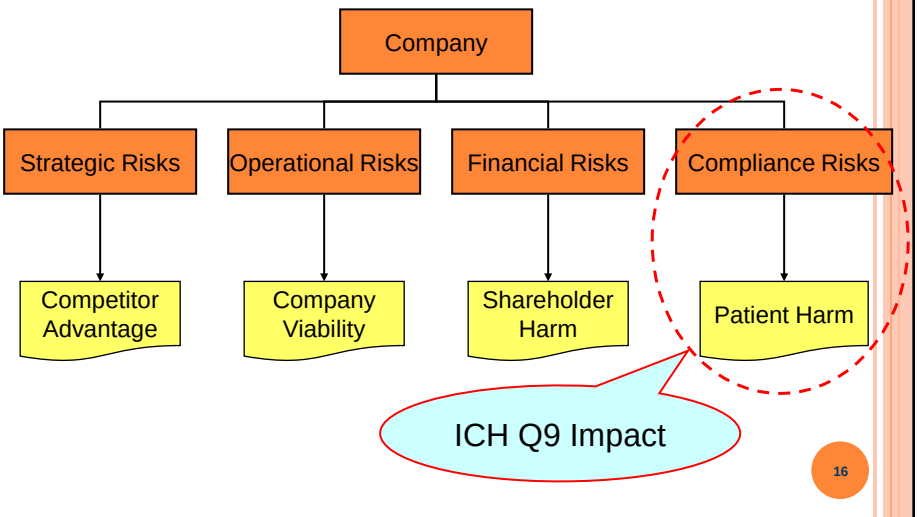


1. Introduction – Risk management is Universal



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2. ICH Q9 – Quality Risk Management (品質風險管理)

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2. ICH Q9 - Scope

This guideline provides
principles & examples of tools
of quality risk management that can be applied to
different aspects of pharmaceutical quality.

These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products

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2. ICH Q9 – Scope 範圍

- Drug substances,
- Drug (medicinal) products,
- Biological and biotechnological products

Including the selection and use of

- **Raw materials**
- **Solvents**
- **Excipients**
- **Packaging and labelling materials**
- **Components**

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2. ICH Q9 – Principles 原則

Two primary principles:

The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient

The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk

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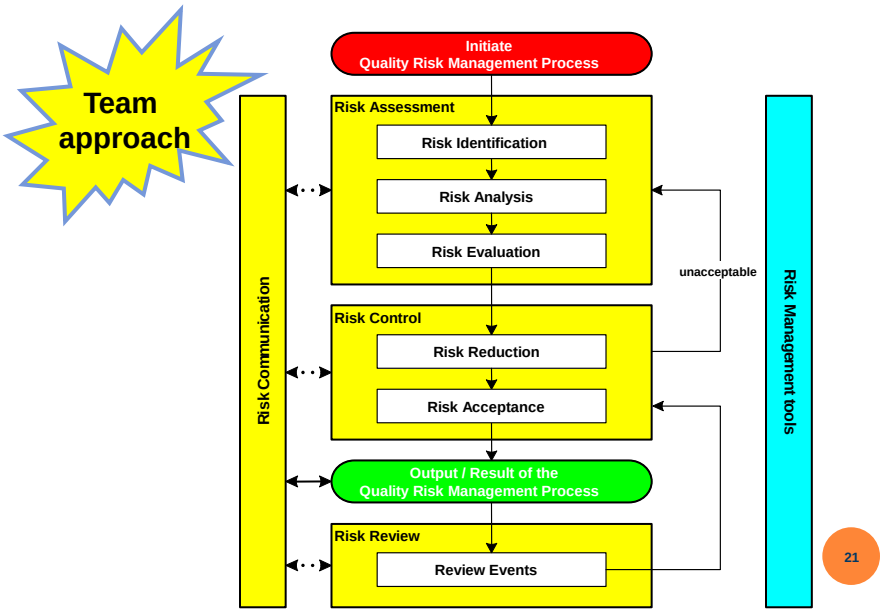
2. ICH Q9 – General process 基本流程



2. ICH Q9 – Responsibilities 責任

Decision makers:
People
with competence and authority
to make a decision

- Ensuring that
  ongoing Quality Risk Management processes operate
- Coordinating
  quality risk management process
  across various functions and departments
- Supporting
  the team approach

Management responsibility

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2. ICH Q9 – Responsibilities

Team approach

- Usually, but not always, undertaken by interdisciplinary teams from areas appropriate to the risk being considered e.g.
  - **Quality unit**
  - **Development**
  - **Engineering / Statistics**
  - **Regulatory affairs**
  - **Production operations**
  - **Business, Sales and Marketing**
  - **Legal**
  - **Medical / Clinical**
  - **&… Individuals knowledgeable of the QRM processes**

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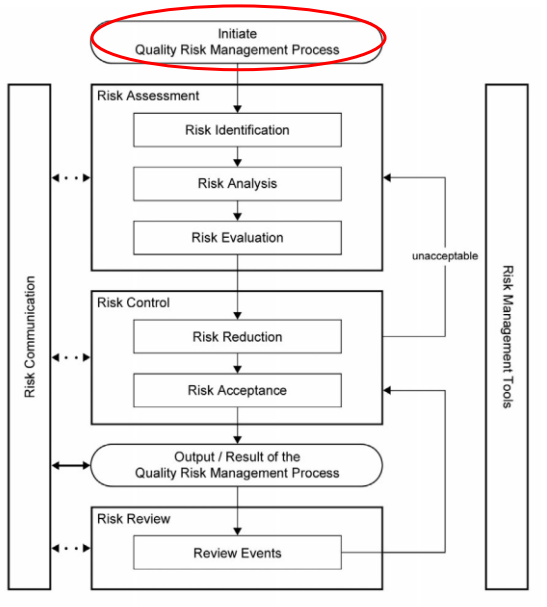
2. ICH Q9 – Initiation 起始



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2. ICH Q9 – Initiation

When to initiate and plan a QRM Process

- First define the question which should be answered (e.g. a problem and/or risk question)
  - **including pertinent assumptions identifying the potential for risk**
- Then assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk
  - **Identify a leader and necessary resources**
  - **Specify a timeline, deliverables and appropriate level of decision making for the QRM process**

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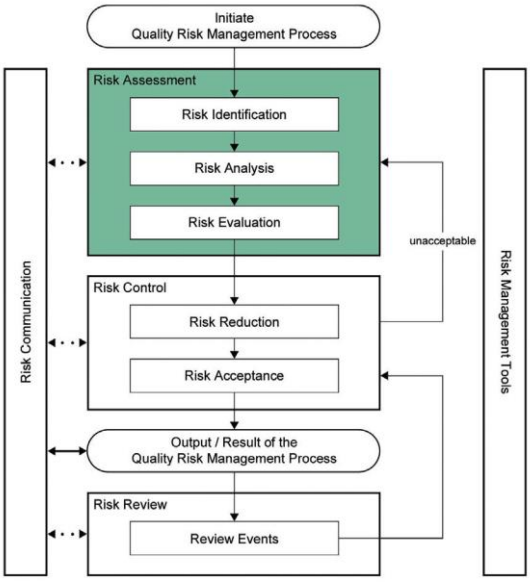
2. ICH Q9 – Risk Assessment 風險評估



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2. ICH Q9 – Risk Assessment 風險評估

3 fundamental questions

- *Risk Identification*
  What might go wrong?
- *Risk Analysis*
  What is the likelihood (probability) it will go wrong?
- *Risk Evaluation*
  What are the consequences (severity)?

Note: People often use terms
"Risk analysis", "Risk assessment" and
"Risk management" interchangeably
which is incorrect!

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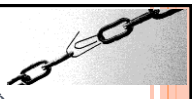
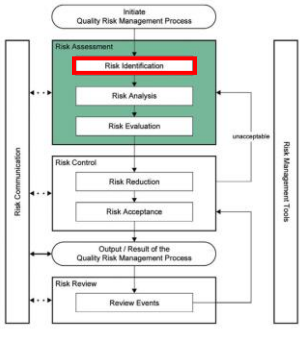
2. ICH Q9 – Risk Assessment



Risk Assessment: Risk Identification 風險辨識

"What might go wrong?"

- A systematic use of information
  to identify hazards
  referring to the risk question or problem
  - **historical data**
  - **theoretical analysis**
  - **informed opinions**
  - **concerns of stakeholders**



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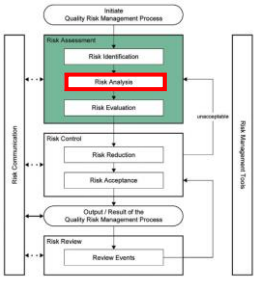
2. ICH Q9 – Risk Assessment

Risk Assessment: Risk Analysis 風險分析

"What is the likelihood it will go wrong?"

- The estimation of the risk associated with the identified hazards.
- A qualitative or quantitative process of linking the likelihood of occurrence and severity of harm
- Consider detectability if applicable (used in some tools)



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2. ICH Q9 – Risk Assessment

Risk Assessment: Risk Evaluation 風險評價

"What is the risk?"

- Compare the identified and analysed risk against given risk criteria
- Consider the strength of evidence for all three of the fundamental questions
  - What might go wrong?
  - What is the likelihood (probability) it will go wrong?
  - What are the consequences (severity)?

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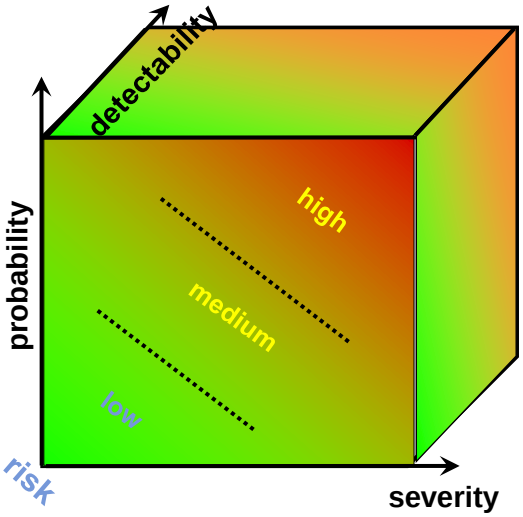
2. ICH Q9 – Risk Assessment

Risk Assessment: Risk Evaluation風險評價

Parameters for evaluating risks



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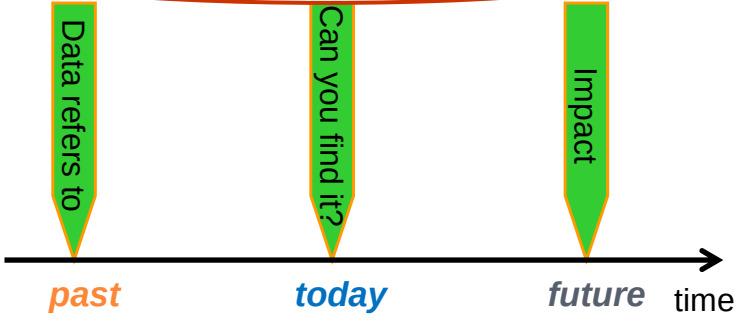
2. ICH Q9 – Risk Assessment

Risk Assessment: Risk Evaluation風險評價

A picture of the life cycle

= Risk Priority Number

Probability x ***Detectability*** x ***Severity***



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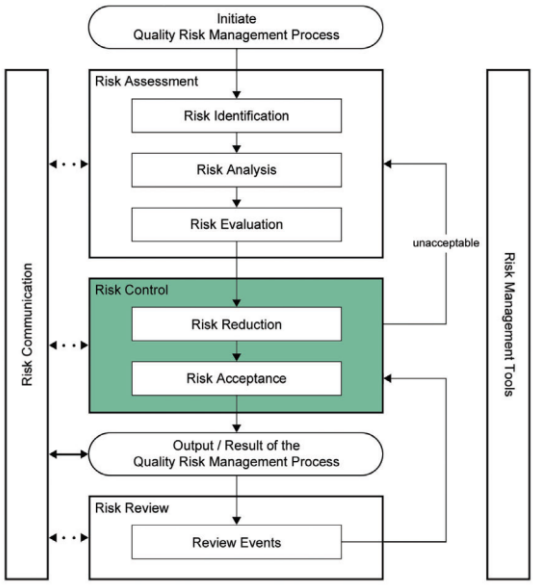
2. ICH Q9 – Risk Control 風險控制



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2. ICH Q9 – Risk Control

Risk Control: Decision-making activity

- **Is the risk above an acceptable level?**
- **What can be done to reduce or eliminate risks?**
- **What is the appropriate balance between benefits, risks and resources?**
- **Are new risks introduced as a result of the identified risks being controlled?**

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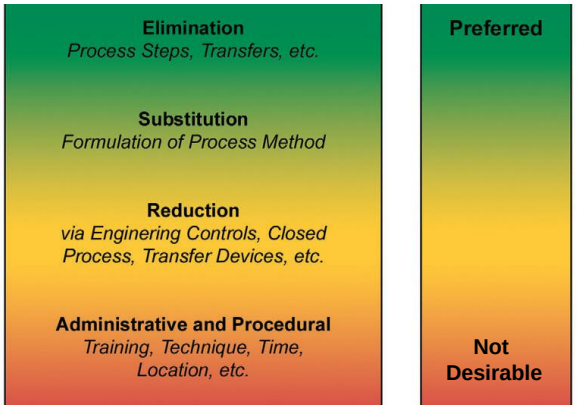
2. ICH Q9 – Risk Control

Risk Control: Risk Reduction 風險降低



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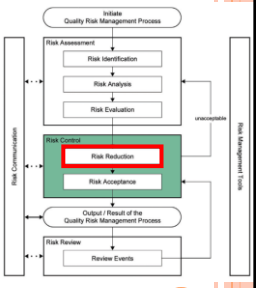

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2. ICH Q9 – Risk Control

Risk Control: Risk Acceptance 風險接受

- **Decision to**
  - > **Accept the residual risk**
  - > **Passively accept non specified residual risks**
- **May require support by (senior) management**
  - > **Applies to both industry and competent authorities**
- **Will always be made on a case-by-case basis**

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2. ICH Q9 – Risk Control

Risk Control: Risk Acceptance風險接受

- Discuss the appropriate balance between benefits, risks, and resources
- Focus on the patients' interests and good science/data
- Risk acceptance **is not**
  - **Inappropriately interpreting data and information**
  - **Hiding risks from management / competent authorities**

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2. ICH Q9 – Risk Control

Risk Control: Risk Acceptance 風險接受

Who has to accept risk?

- Decision Maker(s)
  - Person(s) with the competence and authority to make appropriate and timely quality risk management decisions
- Stakeholder
  - Any individual, group or organization that can …be affected by a risk
  - Decision makers might also be stakeholders
  - The primary stakeholders are the patient, healthcare professional, regulatory authority, and industry
  - The secondary stakeholders are patient associations, public opinions, politicians

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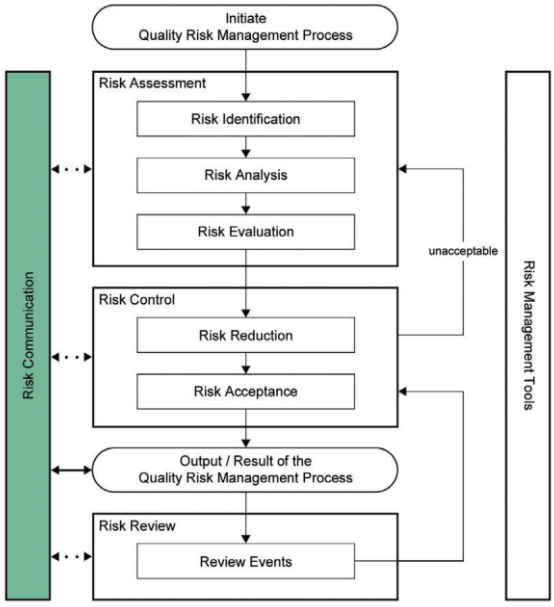
2. ICH Q9 – Risk Communication 風險溝通



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2. ICH Q9 – Risk Communication

- Bi-directional sharing of information about risk and risk management between the decision makers and others
- Communicate at any stage of the QRM process
- Communicate and document the output/result of the QRM process appropriately
- Communication need not be carried out for each and every individual risk acceptance
- Use existing channels as specified in regulations, guidance and SOP's

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2. ICH Q9 – Risk Communication

- Exchange or sharing of information, as appropriate
- Sometimes formal sometimes informal
  - **Improve ways of thinking and communicating**
- Increase transparency

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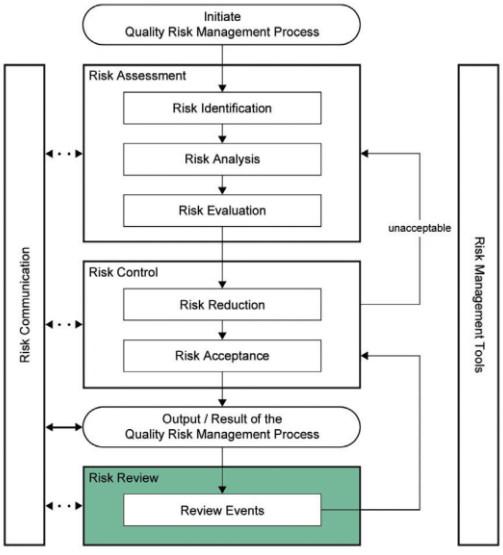
2. ICH Q9 – Risk Review 風險評審



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2. ICH Q9 – Risk Review 風險評審

Risk review: Review Events

- Review the output / results of the QRM process
- Take into account new knowledge and experience
- Utilise for planned or unplanned events
- Implement a mechanism to review or monitor events
- Reconsideration of risk acceptance decisions, as appropriate

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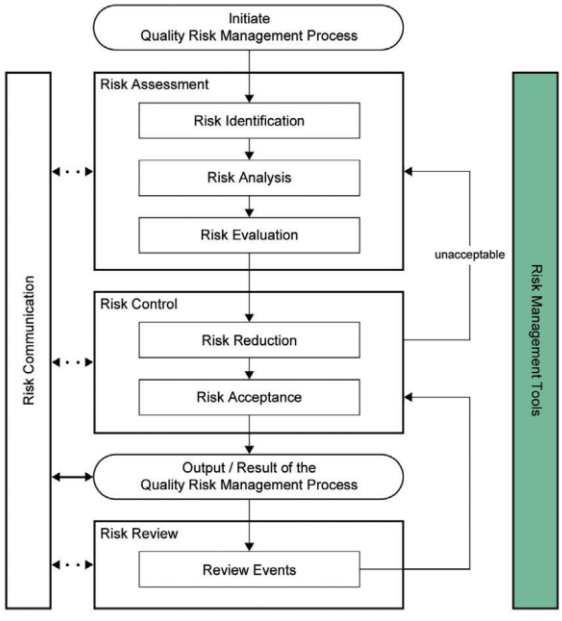
2. ICH Q9 – Risk Management Tools 風險管理工具



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2. ICH Q9 – Risk Management Tools

One method "all inclusive"?

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2. ICH Q9 – Risk Management Tools

- Supports science-based decisions
- A great variety are listed but other existing or new ones might also be used
- No single tool is appropriate for all cases
- Specific risks do not always require the same tool
- Using a tool the level of detail of an investigation will vary according to the risk from case to case
- Different companies, consultancies and competent authorities may promote use of different tools based on their culture and experiences

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2. ICH Q9 – Risk Management Tools

- Supports a scientific and practical approach to decision-making
- Accomplishing steps of the QRM process
  - **Provides documented, transparent and reproducible methods**
  - **Assessing current knowledge**
  - **Assessing probability, severity and sometimes detectability**

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2. ICH Q9 – Risk Management Tools

- Failure Mode Effects Analysis (FMEA)
  - Break down large complex processes into manageable steps
- Failure Mode, Effects and Criticality Analysis (FMECA)
  - FMEA & links severity, probability & detectability to criticality
- Fault Tree Analysis (FTA)
  - Tree of failure modes combinations with logical operators
- Hazard Analysis and Critical Control Points (HACCP)
  - Systematic, proactive, and preventive method on criticality
- Hazard Operability Analysis (HAZOP)
  - Brainstorming technique
- Preliminary Hazard Analysis (PHA)
  - Possibilities that the risk event happens
- Risk ranking and filtering
  - Compare and prioritize risks with factors for each risk

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應用風險管理於GMP各領域

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1. Why we need risk assessment (風險評估)?

26.09.2018

How FDA will prioritise Inspections

The US Food and Drug Administration (FDA) has published a Manual of Policies and Procedures (MAPP) describing how the agency will prioritise surveillance inspections of pharmaceutical manufacturing sites.

According to a statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's global efforts to help assure product quality and transparency at foreign drug manufacturing facilities, "*FDA's inspections program is a large-scale endeavour*":
Last year, more than 5.000 routine surveillance inspections were performed with more than 3.000 inspections outside the US. This is a lot of work and as other agencies, FDA needs to prioritise actions. FDA will use a "*risk-based site selection model to ensure that inspectional resources are allocated in the most efficient and appropriate manner to protect patient health*". The inspection frequency will be based on the potential risk of products and processes for patients - and not on the location of the site.

The so called **Site Selection Model (SSM)** will cover sites according the CDER Catalog of Manufacturing Sites, as determined by section 510 of the FD&C Act. This embraces sites that commercially manufacture finished pharmaceuticals (drug products), in-process materials, or active pharmaceutical ingredients (API; drug substance) for use in a drug intended for humans. Drugs intended for use only in clinical trials (investigational medicinal products, IMP) are not included; these sites may be inspected "*when deemed necessary*".

As a result, a **Site Surveillance Inspection List (SSIL)** will be created, prioritising sites for surveillance inspections. The number of sites will also depend on FDA's capacity and resources. But it will be mainly based on defined risk factors:

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1. Why we need risk assessment (風險評估)?

Medicines & Healthcare products Regulatory Agency

Guidance

Good manufacturing practice and good distribution practice

Published 18 December 2014

Types of inspection

Inspections under the risk-based compliance programme

Every manufacturer and wholesaler has a risk rating or score and we prioritise inspections for those with the highest ratings or scores. You will be told about these inspections in advance, although under the short-notice inspection programme we may send little or no notification. At the inspection, GMP and/or GDP inspectors examine the systems used to manufacture and/or distribute medicines.

Your GMP rating is based on:

- your compliance report
- internal information about previous inspection history
- organisational changes

You can't appeal against your rating.

An increase in risk will be peer reviewed by a GMP operations manager, a member of the compliance management team (CMT) or a GMP expert inspector before being finalised.

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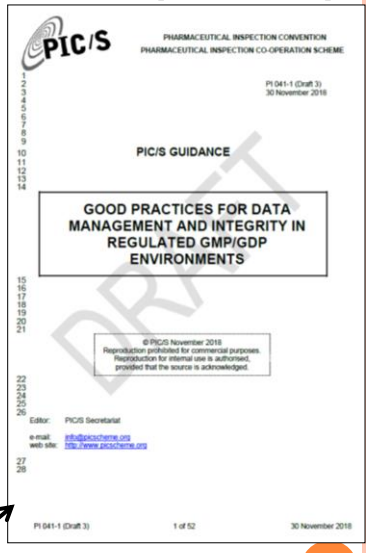
You will be given a full copy of the reasons for your risk rating once the inspection has closed.

1. Why we need risk assessment (風險評估)?

- PIC/S issued a draft guidance on **Data Integrity** (10Aug2016). The guidance is quite detailed and mentions Quality Culture, management review, data criticality, **risk management** and more.


PIC/S

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 041-1 (Draft 3)
30 November 2018

PIC/S GUIDANCE

GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS

DRAFT

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Editor: PIC/S Secretariat
e-mail: info@picscheme.org
web site: http://www.picscheme.org

PI 041-1 (Draft 3) 1 of 52 30 November 2018

Draft 3, published in 30Nov2018

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1. Why we need risk assessment (風險評估)?

- EMA released 23 questions and answers on data integrity. The stakeholder advice includes measures that ensure data integrity and minimize risks at all stages of the data lifecycle in pharmaceutical quality systems.

Data integrity (NEW August 2016)

Back to top

Expand all items in this list

- Data integrity
- 1. How can data risk be assessed?
- 2. How can data criticality be assessed?
- 3. What does 'Data Lifecycle' refer to?
- 4. Why is 'Data lifecycle' management important to ensure effective data integrity measures?
- 5. What should be considered when reviewing the 'Data lifecycle'?
- 6. 'Data lifecycle': What risks should be considered when assessing the generating and recording of data?
- 7. 'Data lifecycle': What risks should be considered when assessing the processing data into usable information?
- 8. 'Data lifecycle': What risks should be considered when checking the completeness and accuracy of reported data and processed information?
- 9. 'Data lifecycle': What risks should be considered when data (or results) are used to make a decision?

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1. Why we need risk assessment (風險評估)?

- EMA released 23 questions and answers on data integrity.

Data integrity

1. How can data risk be assessed?

Data risk assessment should consider the vulnerability of data to involuntary or deliberate amendment, deletion or recreation. Control measures which prevent unauthorised activity and increase visibility / detectability can be used as risk mitigating actions.

Examples of factors which can increase risk of data integrity failure include complex, inconsistent processes with open-ended and subjective outcomes. Simple tasks which are consistent, well-defined and objective lead to reduced risk.

Risk assessment should include a business process focus (e.g. production, QC) and not just consider IT system functionality or complexity. Factors to consider include:

- Process complexity
- Process consistency, degree of automation /human interface
- Subjectivity of outcome / result
- Is the process open-ended or well defined

This ensures that manual interfaces with IT systems are considered in the risk assessment process. Computerised system validation in isolation may not result in low data integrity risk, in particular when the user is able to influence the reporting of data from the validated system.

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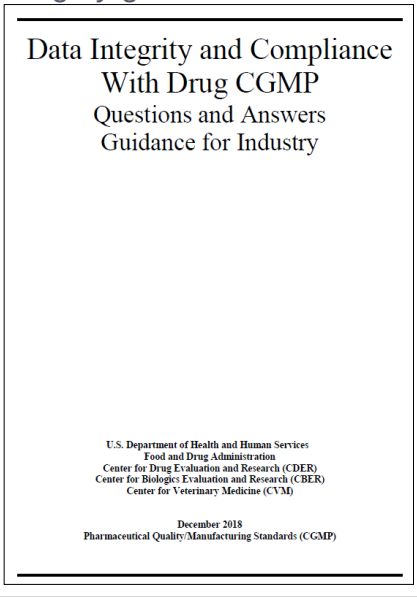
1. Why we need risk assessment (風險評估)?

- FDA data integrity guidance in Dec 2018.



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1. Why we need risk assessment (風險評估)?

- FDA data integrity guidance in Dec 2018.

I. INTRODUCTION

The purpose of this guidance is to clarify the role of data integrity in current good manufacturing practice (CGMP) for drugs, as required in 21 CFR parts 210, 211, and 212. Unless otherwise noted, the term *CGMP* in this guidance refers to CGMPs for drugs (including biologics). FDA's authority for CGMP comes from section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Part 210 covers Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General; part 211 covers Current Good Manufacturing Practice for Finished Pharmaceuticals; and part 212 covers Current Good Manufacturing Practice for Positron Emission Tomography (PET) Drugs. All citations to parts 211 and 212 in this document pertain to finished pharmaceuticals and PET drugs, but these requirements are also consistent with Agency guidance on CGMP for active pharmaceutical ingredients with respect to data integrity.[2] This guidance provides the Agency's current thinking on the creation and handling of data in accordance with CGMP requirements.

FDA expects that all data be reliable and accurate (see the "Background" section). CGMP regulations and guidance allow for flexible and risk-based strategies to prevent and detect data integrity issues. Firms should implement meaningful and effective strategies to manage their data integrity risks based on their process understanding and knowledge management of technologies and business models.[3]

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1. Why we need risk assessment (風險評估)?

On 01Mar2015, the EU will have new GMP regulations that address cross contamination. Chapters 3 and 5 of Volume 4 of the EudraLex have been updated.

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL
Health systems and products
Medicinal products – quality, safety and efficacy

Brussels, 13 August 2014

EudraLex

The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Part 1

Deadline for coming into operation: 1 March 2015. However, the toxicological evaluation mentioned in section 20 has to be carried out:

[a] In January 2015 the deadline for coming into operation was adapted with regard to the toxicological evaluation to align with the coming effect of the EMA guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. Furthermore, correction of the reference in footnote 2 took place.

Commission Européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel – Belgium. Telephone: (32-2) 299 11 11

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1. Why we need risk assessment (風險評估)?

On 01Mar2015, the EU will have new GMP regulations that address cross contamination. Chapters 3 and 5 of Volume 4 of the EudraLex have been updated.

5.20 A Quality Risk Management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the products manufactured. Factors including; facility/equipment design and use, personnel and material flow, microbiological controls, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from the evaluation of the products should also be taken into account. The outcome of the Quality Risk Management process should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product or product family. This may include dedicating specific product contact parts or dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a

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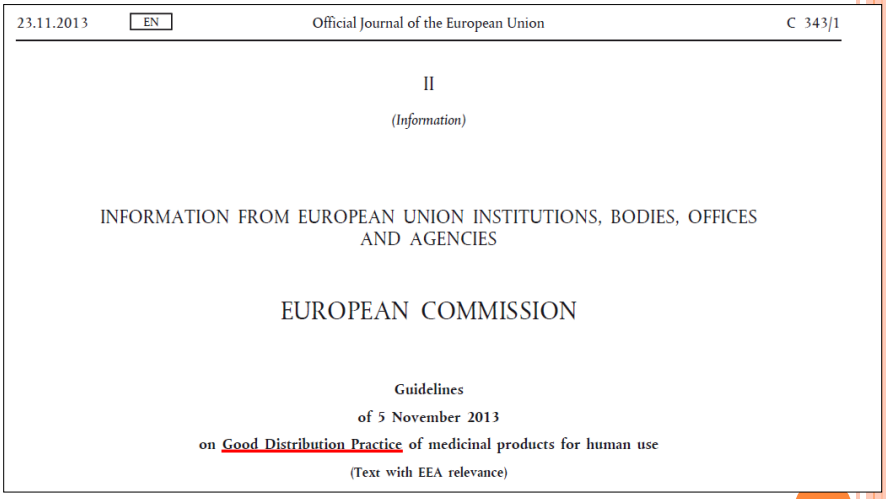
1. Why we need risk assessment?



23.11.2013 EN Official Journal of the European Union C 343/1

II

(Information)

INFORMATION FROM EUROPEAN UNION INSTITUTIONS, BODIES, OFFICES AND AGENCIES

EUROPEAN COMMISSION

Guidelines

of 5 November 2013

on Good Distribution Practice of medicinal products for human use

(Text with EEA relevance)

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1. Why we need risk assessment?

CHAPTER 1 — QUALITY MANAGEMENT

1.1. **Principle**

Wholesale distributors must maintain a quality system setting out responsibilities, processes and risk management principles in relation to their activities ([1]). All distribution activities should be clearly defined and systematically reviewed. All critical steps of distribution processes and significant changes should be justified and where relevant validated. The quality system is the responsibility of the organisation's management and requires their leadership and active participation and should be supported by staff commitment.

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1. Why we need risk assessment?

1.5. **Quality risk management**

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of medicinal products. It can be applied both proactively and retrospectively.

Quality risk management should ensure that the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient. The level of effort, formality and documentation of the process should be commensurate with the level of risk. Examples of the processes and applications of quality risk management can be found in guideline Q9 of the International Conference on Harmonisation ('ICH').

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1. Why we need risk assessment?

9.1. **Principle**
It is the responsibility of the supplying wholesale distributor to protect medicinal products against breakage, adulteration and theft and to ensure that temperature conditions are maintained within acceptable limits during transport.

Regardless of the mode of transport, it should be possible to demonstrate that the medicines have not been exposed to conditions that may compromise their quality and integrity. A risk-based approach should be utilised when planning transportation.

9.2.5
Risk assessment of delivery routes should be used to determine where temperature controls are required. Equipment used for temperature monitoring during transport within vehicles and/or containers, should be maintained and calibrated at regular intervals at least once a year.
See sections 9.3.2 and 9.4.4 for more detail.

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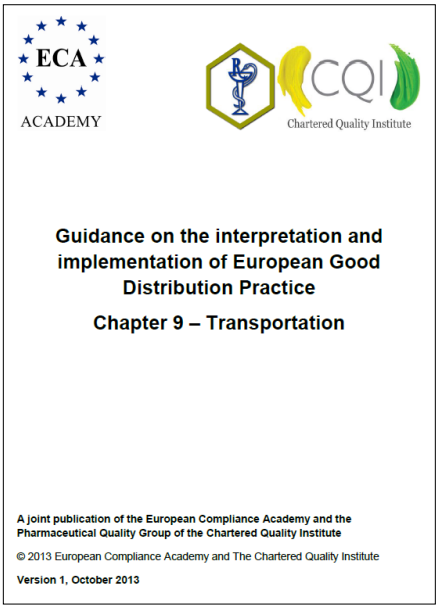
1. Why we need risk assessment?



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1. Why we need risk assessment?

Preface

It is of key importance that medicinal products are not only made to a high quality in accordance with Good Manufacturing Practice, but that the quality and integrity of these products are maintained through the entire supply chain to the patient. This is where Good Distribution Practice (GDP) comes into play.

The distribution network for medicinal products is often complex, involving many different parties. In addition to the challenges associated with this complexity, there is also a growing threat from criminal activities seeking to introduce falsified medicines into the legal supply chain. The European regulators recognised several years ago that there was a need to update the content of the 1994 GDP guideline to take into account advancements in practices and changes in legislation since it was issued. A consultation draft was issued in mid 2011 and, following the receipt of many comments from interested parties, a final revised version was issued in March 2013 with an effective date of 8 September 2013.

The new guideline has a much stronger focus on the quality system with clear responsibilities and processes and the application of risk management principles. More detailed guidance is given on most elements. New chapters relating to transportation and specific provisions for brokers have been added.

1. Why we need risk assessment?

01.10.2019

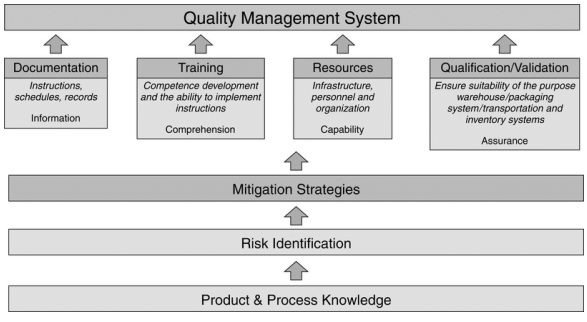
ECA Academy
Your cGMP/GDP Information Source

USP revises Storage and Transport Chapters

USP ⟨1079⟩ GOOD STORAGE AND DISTRIBUTION PRACTICES FOR DRUG PRODUCTS

→

USP ⟨1079⟩ **RISK** AND **MITIGATION** STRATEGIES FOR THE STORAGE AND TRANSPORTATION OF FINISHED DRUG PRODUCTS



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1. Why we need risk assessment?

GENERAL Q&AS ON GOOD DISTRIBUTION PRACTICES (GDP)

As a manufacturer of finished medicinal products, do I need to audit all transport organizations, all warehouses and all wholesalers who will handle my products? What about transportation hubs e.g. at airports. There might be hundreds of such facilities.

The Current EU GDP requires manufacturers to have audited and approved all their outsourced activities and have a technical/quality agreement with their service providers. The approach to selection and approval of these facilities should be supported by risk assessment, companies can use shared audits or 'paper audit' depending on the complexity of operations and sensitivity of the products involved.

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1. Why we need risk assessment?

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1. Why we need risk assessment?

Chapter 1 - Deficiency examples

- At least 8 overdue CAPA (ranging from 59 days to 242 days overdue) were observed to have been closed the day before the inspection.
- Two overdue CAPA were open at the time of the inspection (186 days and 60 days overdue).
- Where134 deviations were raised between November 2015 and February 2016, no CAPA were raised.
- Effective monitoring of CAPA was not in place as numerous CAPA with different due dates could be recorded on a single form but only the latest date was tracked.
- The review of effectiveness of CAPAs was identified as being part of Management Review, however there was insufficient detail describing this process and the process was not risk based as the Management Review was only carried out once a year.

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1. Why we need risk assessment?

Chapter 1 - Deficiency examples

- The management team failed to ensure an effective implementation of the quality systems and to identify opportunities for continual improvement of components, processes and system itself.
- The current reporting method on quality metrics did not sufficiently identify and allow monitoring and assessing the effective implementation of the quality systems. For example, the open and overdue items were not reported for discussion.
- The outstanding quality items reported in the management review meetings were not challenged to identify the root cause for the delay. Risk assessments had not been performed or formally documented to assess the impact on patient safety and the effectiveness of the PQS as a result of choosing to delay addressing the overdue actions.

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1. Why we need risk assessment?

Chapter 1 - Deficiency examples

Deficiencies related to change control management:

- There was insufficient detail recorded to describe the nature of the change and the actions to be carried out.
- There is no definition of which moderate level change controls would require a risk assessment and regulatory affairs review and which would not.
- There is no post implementation review of the effectiveness of change control actions.
- Changes were implemented outside of the company's Change Control procedure.
- Procedures for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification were not robust.
- There was no documented requirement for a post implementation effectiveness check to be performed.

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1. Why we need risk assessment?

Chapter 5 - Deficiency examples

- There was no instruction to prevent the use of the raw materials dispensing booth whilst the dispensing isolator was being used.
- There were cracks in the vinyl around the mist shower drain. This would create a trap point which could cause the accumulation of chemical and microbial contamination.
- Equipment used to manufacture high potent materials was not verified as clean prior to removal to the general storage area.
- The FMEA risk assessment had failed to demonstrate adequate risk mitigation by referring to SOPs without detailing or assessing how controls were implemented.

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3. MHRA (Europe/UK) QRM Q&A

The GMP Questions & Answers Guide Version 2.0

The GMP Questions & Answers Guide

- GMP Advisor -

Version 02 of March 2020

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3. MHRA (Europe/UK) QRM Q&A

1. Do all inspections cover the quality risk management process?

Yes, quality risk management (QRM) is a requirement of Chapter 1 of the EU GMP Guide Part I, II and III. Inspectors will review the QRM system as part of the Quality Systems section of the inspection (along with complaints, recalls, deviations, and product quality reviews etc.).

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3. MHRA (Europe/UK) QRM Q&A

3. Should a company have a procedure to describe how it approaches QRM related to manufacture and GMP?

Yes, the procedure should be integrated with the quality system and apply to planned and unplanned risk assessments. The standard operating procedure (SOP) should define how the management system operates and its general approach to both planned and unplanned risk management.

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3. MHRA (Europe/UK) QRM Q&A

4. Is it acceptable to link quality risk management with cost saving measures?

The expectation of QRM is to assess risks to the medicinal product and patient and manage these to an acceptable level. If this can be achieved in a more cost effective manner while maintaining or reducing risk to the product and patient then this is acceptable. However inappropriate risk assessment and mitigation in order to achieve cost savings is not appropriate.

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3. MHRA (Europe/UK) QRM Q&A

5. Should sites have a formal risk register and management process?

There is no formal requirement in Annex III for a risk register however MHRA consider that it is helpful to the implementation and ongoing management of QRM that a risk register is established.

A management process should be in place to review QRM and the findings and status from risk assessments – this may be incorporated into the quality management review process.

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3. MHRA (Europe/UK) QRM Q&A

7. Do formal tools and a full report have to be issued for every risk assessment?

The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

Inspector's pragmatism will be directly related to the nature of the risk with increasingly more formality and detail required for more significant risk

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3. MHRA (Europe/UK) QRM Q&A

10. Should we expect there to be no risk to patient safety as a conclusion to a risk assessment?

In reality there is always a degree of risk in all situations but risk reduction measures should minimize the probability and severity to an acceptable level of assurance.

Companies should take a holistic view and be mindful that critical issues often occur where multiple failures in systems occur together so risk reduction plans should be sufficiently robust to tackle such potential.

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3. MHRA (Europe/UK) QRM Q&A

12. How should risk assessments be controlled?

Risk assessments should be controlled within a defined document management system.

Frequency of review should be appropriate for the nature of the process. Such risk assessments should be seen as living documents that are visible and subject to change as and when required. Risk assessments that were conducted as one off activities to assess a situation that will not recur need not be controlled in a 'live' manner but must be documented, approved and retained

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3. MHRA (Europe/UK) QRM Q&A

14. Scoring in risk assessments is subjective, is there danger that risk assessments may be manipulated to draw desired conclusions?

The scoring system and trigger points for risk reduction are subjective. However as important as the scores in risk assessments is the rationale for the score. If supported by factual evidence it should be more obvious what risk control and reduction measures are required

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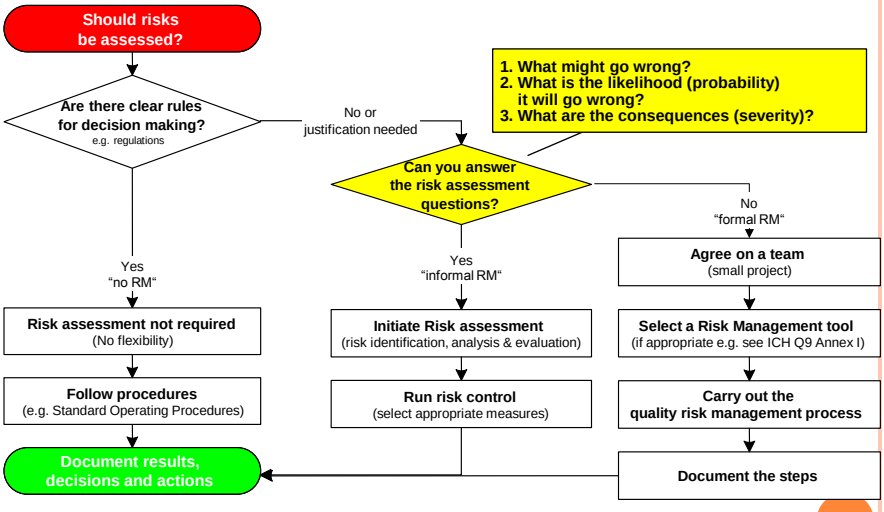
4. Risk Assessment Tools

- When to apply Risk Assessment / QRM?



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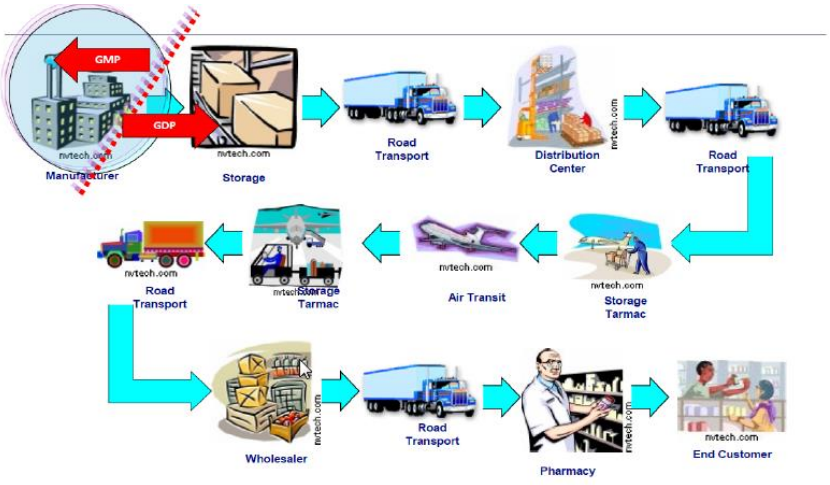
Based on K. Connelly, AstraZeneca, 2005

4. Risk Assessment Tools – Process map

Transportation QRM



4. Risk Assessment Tools – Process map

Manufacturing of ^{18}F-FDG

- Synthesize of ^{18}F-FDG
  - Radionuclide production (Fluorine vs Fluoride)
  - Separation of Fluoride ion from the target material
  - Fluorination (Radiolabeling)
  - Purification of radiopharmaceutical (FDG)
- Dispensing of ^{18}F-FDG

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4. Risk Assessment Tools – FMEA 失效模式

- Identify each way the process can fail
- Identify the possible consequences of each failure mode
- Assign numerical rankings

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4. Risk Assessment Tools – FMEA

- **Quantitation of Risk: Severity 嚴重性**

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ low yield
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action

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4. Risk Assessment Tools – FMEA

- **Quantitation of Risk: Probability 發生率**

Score	Risk Probability
1	**Not observed, extremely unlikely to occur** (i.e. 1 per 5 years or < 0.5% of the time)
3	**Not anticipated, but possible** (i.e. 1 per year or 0.5% to 1.5% of the time)
5	**Failure observed occasionally, likely to occur** (i.e. 1 per month – quarter or 1.5% to 10% of the time)
7	**Very likely to occur, almost certain** (i.e. 1 per week - month or > 10% of the time)

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4. Risk Assessment Tools – FMEA

- **Quantitation of Risk: Probability 發生率**

Score	Risk Probability
1	**Not observed, extremely unlikely to occur/ proactive control or maintenance**
3	**Not anticipated, but possible/ passive control or maintenance**
5	**Failure observed occasionally, likely to occur/ no control or maintenance**
7	**Very likely to occur, almost certain/ no control or maintenance with easy break nature**

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4. Risk Assessment Tools – FMEA

- **Quantitation of Risk: Detectability** 可偵測性

Score	Risk Detectability
1	**Almost certain- Failure detected in every instance** (i.e. automatic detection, in process test, and manual detection with several checking points, include at least one witness check)
3	**Very likely detection** (i.e. manual detection with several checking points, not include witness check, error can be detected in the later manufacturing step)
5	**Moderate chance of detection** (i.e. manual detection with MBR reviewer)
7	**Essentially Undetectable**

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4. Risk Assessment Tools – FMEA

Risk Evaluation Score
(Severity X Probability X Detectability = RPN)

Decrease Detectability

Increase Severity & Probability

	1	3	5	7
1	1	3	5	7
3	3	9	15	21
5	5	15	25	35
6	6	18	30	42
7	7	21	35	49
9	9	27	45	63
15	15	45	75	105
18	18	54	90	126
21	21	63	105	147
27	27	81	135	189
30	30	90	150	210
42	42	126	210	294
45	45	135	225	315
63	63	189	315	441

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

90

4. Risk Assessment Tools – FMEA

Risk Evaluation – Risk Acceptance?

Decrease Detectability

Increase Severity & Probability

	1	3	5	7
1	1	3	5	7
3	3	9	15	21
5	5	15	25	35
6	6	18	30	42
7	7	21	35	49
9	9	27	45	63
15	15	45	75	105
18	18	54	90	126
21	21	63	105	147
27	27	81	135	189
30	30	90	150	210
42	42	126	210	294
45	45	135	225	315
63	63	189	315	441

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

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4. Risk Assessment Tools – FMEA

How to design a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

Risk sources (phenomena and root cause)

Based on the historical data (e.g. deviations), interview, experience, and etc.

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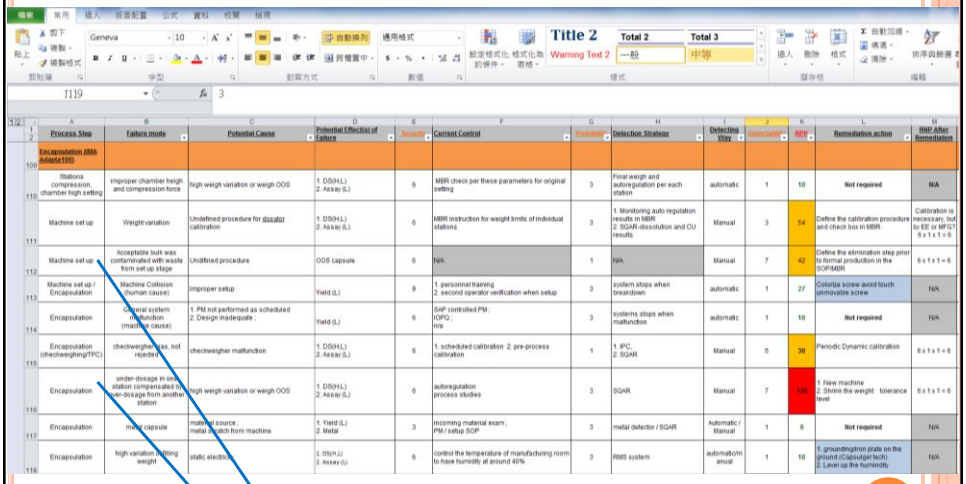
4. Risk Assessment Tools – FMEA

How to create a FMEA table



	Process Step	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation
109	Encapsulation (IMA Adapta1001)												
110	Stations compression, chamber high setting	improper chamber heigh and compression force	high weigh variation or weigh OOS	1. DS(HL) 2. Assay (L)	6	MBR check per these parameters for original setting	3	Final weigh and autoregulation per each station	automatic	1	18	Not required	N/A
111	Machine set up	Weight variation	Undefined procedure for dosator calibration	1. DS(HL) 2. Assay (L)	6	MBR instruction for weight limits of individual stations	3	1. Monitoring auto regulation results in MBR 2. SQAR-dissolution and CU results	Manual	3	54	Define the calibration procedure and check box in MBR	Calibration is necessary, but to EE or MFG? 6 x 1 x 1 = 6
112	Machine set up	Acceptable bulk was contaminated with waste from set up stage	Undefined procedure	OOS capsule	6	N/A	1	N/A	Manual	7	42	Define the elimination step prior to formal production in the SOP/MBR	6 x 1 x 1 = 6
113	Machine set up / Encapsulation	Machine Collision (human cause)	improper setup	Yield (L)	9	1. personnel training 2. second operator verification when setup	3	system stops when breakdown	automatic	1	27	Colorize screw avoid touch unmovable screw	N/A
114	Encapsulation	General system malfunction (machine cause)	1. PM not performed as scheduled 2. Design inadequate ;	Yield (L)	6	SAP controlled PM ; IOPQ ; n/a	3	systems stops when malfunction	automatic	1	18	Not required	N/A
115	Encapsulation (checkweighing/TPC)	checkweigher bias, not rejected	checkweigher malfunction	1. DS(HL) 2. Assay (L)	6	1. scheduled calibration 2. pre-process calibration	1	1. IPC, 2. SQAR	Manual	5	30	Periodic Dynamic calibration	6 x 1 x 1 = 6
116	Encapsulation	under-dosage in one station compensated by over-dosage from another station	high weigh variation or weigh OOS	1. DS(HL) 2. Assay (L)	6	autoregulation process studies	3	SQAR	Manual	7	126	1. New machine 2. Shrink the weight tolerance level	6 x 1 x 1 = 6
117	Encapsulation	metal capsule	material source ; metal scratch from machine	1. Yield (L) 2. Metal	3	incoming material exam ; PM / setup SOP	3	metal detector / SQAR	Automatic / Manual	1	9	Not required	N/A
118	Encapsulation	high variation in filling weight	static electric	1. DS(HL) 2. Assay (L)	6	control the temperature of manufacturing room to have humidity at around 45%	3	RMS system	automatic/manual	1	18	1. groundingiron plate on the ground (Capsulgel tech) 2. Level up the humidity	N/A

Machine setup

Encapsulation

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4. Risk Assessment Tools – FMEA

How to create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

Evaluation standard for Severity

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4. Risk Assessment Tools – FMEA

During oven drying process

Example 1, Operator forgets to sign on MBR: Severity = 1

Example 2, Operator forgets to discharge all product: Severity = 3

Example 3, Wrong inlet air temperature (LOD OOS): Severity = 6

Example 4, Wrong inlet air temperature → high toxic impurity: Severity = 9

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ low yield
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action

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4. Risk Assessment Tools – FMEA

How to create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

Evaluation standard for Probability

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4. Risk Assessment Tools – FMEA

During oven drying process: LOD OOS

Example 1, 1st OOS over 10 years : Probability = 1

Example 2, 1st OOS in the recent 100 lots: Probability = 3

Example 3, 1st PPQ lot with OOS: Probability = 7

Score	Risk Probability
1	**Not observed, extremely unlikely to occur** (i.e. 1 per 5 years or < 0.5% of the time)
3	**Not anticipated, but possible** (i.e. 1 per year or 0.5% to 1.5% of the time)
5	**Failure observed occasionally, likely to occur** (i.e. 1 per month – quarter or 1.5% to 10% of the time)
7	**Very likely to occur, almost certain** (i.e. 1 per week - month or > 10% of the time)

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4. Risk Assessment Tools – FMEA

During oven drying process: LOD OOS

Example 1, A backup dual temp. control system with PM program: Severity = 1

Example 2, A solo temp. control system with PM program: Severity = 3

Example 3, A solo temp. control system without PM program: Severity = 5

Example 4, A solo temp. control system with rusty steam piping and no PM program : Severity = 7

Score	Risk Probability
1	**Not observed, extremely unlikely to occur/ proactive control or maintenance**
3	**Not anticipated, but possible/ passive control or maintenance**
5	**Failure observed occasionally, likely to occur/ no control or maintenance**
7	**Very likely to occur, almost certain/ no control or maintenance with easy break nature**

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4. Risk Assessment Tools – FMEA

How to create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

Evaluation standard for Detectability

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4. Risk Assessment Tools – FMEA

During oven drying process: temp. excursion

Example 1, temp. sensor with alarm: Detectability = 1

Example 2, QA and Operator checking: Detectability = 3

Example 3, Operator checking: Detectability = 5

Example 4, N/A: Detectability = 7

Score	Risk Detectability
1	**Almost certain- Failure detected in every instance** (i.e. automatic detection, in process test, and manual detection with several checking points, include at least one witness check)
3	**Very likely detection** (i.e. manual detection with several checking points, not include witness check, error can be detected in the later manufacturing step)
5	**Moderate chance of detection** (i.e. manual detection with MBR reviewer)
7	**Essentially Undetectable**

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4. Risk Assessment Tools – FMEA

How to create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

Risk Control: implement control actions to reduce risk (**Risk Reduction**)

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4. Risk Assessment Tools – FMEA

How to create a FMEA table

During oven drying process: air born cross contamination issue

Elimination *Process Steps, Transfers, etc.*	Do not mfg this product
Substitution *Formulation of Process Method*	Change oven drying to FBD drying
Reduction *via Enginering Controls, Closed Process, Transfer Devices, etc.*	Use dust collector in the process
Administrative and Procedural *Training, Technique, Time, Location, etc.*	Revise SOP for personnel training

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4. Risk Assessment Tools – FMEA

How to create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)

	1	3	5	7
1	1	3	5	7
3	3	9	15	21
5	5	15	25	35
6	6	18	30	42
7	7	21	35	49
9	9	27	45	63
15	15	45	75	105
18	18	54	90	126
21	21	63	105	147
27	27	81	135	189
30	30	90	150	210
42	42	126	210	294
45	45	135	225	315
63	63	189	315	441

Risk Control: reduce risk level to acceptable level (**Risk acceptance**)

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5. Case Study I – Warehouse Temperature

Create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Temp.	Temperature variation leads to product exposure under unacceptable conditions	Environment-al effect (day and night switch)	Impurity, AS									

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5. Case Study I – Warehouse Temperature

Create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Temp.	Temperature variation leads to product exposure under unacceptable conditions	Environment-al effect (day and night switch)	Impurity, AS	6								

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action

5. Case Study I – Warehouse Temperature

Create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Temp.	Temperature variation leads to product exposure under unacceptable conditions	Environment-al effect (day and night switch)	Impurity, AS	6	Warehouse HVAC control system	1						

Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect

5. Case Study I – Warehouse Temperature

Create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Temp.	Temperature variation leads to product exposure under unacceptable conditions	Environment-al effect (day and night switch)	Impurity, AS	6	Warehouse HVAC control system	1	Temperature monitored by RMS	Automatic	1			

Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

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5. Case Study I – Warehouse Temperature

Create a FMEA table

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Temp.	Temperature variation leads to product exposure under unacceptable conditions	Environment-al effect (day and night switch)	Impurity, AS	6	Warehouse HVAC control system	1	Temperature monitored by RMS	Automatic	1	6	Not required	N/A

Risk Evaluation Score:

Severity X Probability X Detectability = RPN

6 X 1 X 1 = 6

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

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5. Case Study II – Warehouse Humidity

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse	Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%											

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5. Case Study II – Warehouse Humidity

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse	Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%											
Humidity	High excursion	Environmental effect (sunny and raining day)	Impurity, AS		N/A		Humidity monitored by RMS	automatic		42		

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action
Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect
Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

5. Case Study III – Warehouse Vibration

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Vibration	Bulk product breakage	Dropping or bumping of the drum	Appearance	1	Bubble wrap application in the inner drum	1	1. Monitored by packaing operator at packaging site 2. Packaging site QA sampling	Manual	3	3	Not required	N/A

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action
Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect
Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

5. Case Study IV – Warehouse Process

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
Impax TW Warehouse Control Spec.: Temperature: 20-25 ℃, Relative humidity: 65%												
Process	Drum or lid cracking	Improper packaging (piling) of the drums leads to drum or lid cracking	Appearance	1	SOP for equipment safety operation process	3	1. Checked by packaing personnel at warehouse personnel 2. Checked by QA at packaging site	Manual	3	9	Not required	N/A

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action
Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect
Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

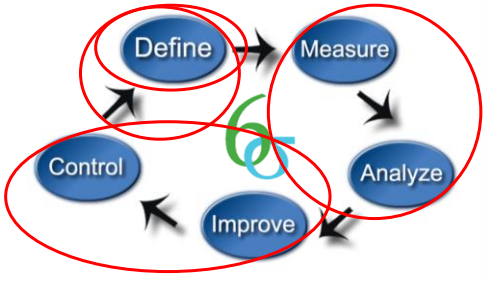
5. Case Study V – Apron Temperature

Category	Failure mode	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	Probability	Detection Strategy	Detecting Way	Detectability	RPN	Remediation action	RNP After Remediation (S x P x D = RPN)
ULD Area Apron in TPE Airport												
Temperature	High excursoin during Summer	Seasonal environmental effect	Impurity, AS	3	1. Night freight during the period of Apr to Oct 2. VUN requested. The time at the apron is controlled in 1-3 hours 3. Insulated packaging to control temperatre variation	5	TT4 monitoring	Automatic	1	15	Not required	N/A

Risk Level	RPN Range
Low	PRN < 30
Medium	30 ≤ RPN < 90
High	90 ≤ RPN

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action
Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect
Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

6. Summary



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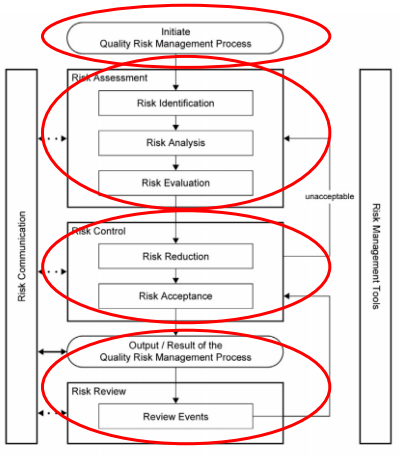

ICH Q9

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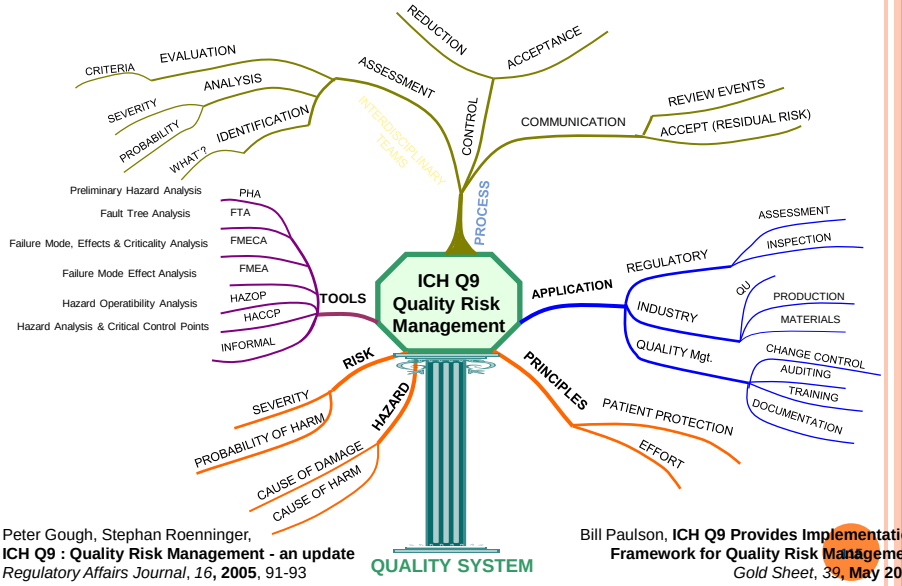
6. Summary



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Gold Sheet, *39*, **May 2005**

ICH Q9 QRM Revisions on Horizon

PDA Letter Jan/Feb 2020

ICH Q9: Quality Risk Management Revisions on Horizon

Rebecca Stauffer, PDA

International Council for Harmonisation of Technical Requirement for Pharmaceuticals for Human Use (ICH) is considering revising portions of Quality Guideline No. 9: *Quality Risk Management* (Q9), though the guideline as a whole will not be rewritten, according to **Stephan Rönninger,** PhD, Director Quality External Affairs, Amgen. He spoke on "15 Years of ICH Q9: Practical Implementation & Pitfalls" at the *2019 PDA Risk Management in the Regulatory Landscape Conference* in Washington, D.C., Dec. 10.

The future revision was discussed during the "questions and answers" following his presentation. Two years ago, he explained, ICH formed an informal quality discussion group to look at all existing guidelines to determine which ones need to go to a maintenance procedure or should be fully revised. Many of the regulatory members of the group expressed an interest in revising ICH Q9.

"It was discussed in the last ICH meeting in Singapore that ICH [Q9] should undergo a revision by a 'development of integrated addendum,'" Roenninger said.

A development integrated addendum according to ICH parlance means only specific sections of the guideline will be targeted for revision, Rönninger explained, but a complete revision is off the table. He said the sections to be revised have yet to be identified and no timeline is available.

During the lunch directly following the Q&A, conference attendees developed a list of recommended revisions to ICH Q9. This list will be published on the Letter website soon. Within PDA, a team will also review the suggestions to potentially respond to ICH.

Stephan Rönninger

Originally published online Dec. 11, 2019

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Thank you for your attention

Questions?

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